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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/364,847	07/30/1999	OLIVER P. PEOPLES	MBX030	9982

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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/364,847	PEOPLES ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 12 May 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *12 May 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attachment*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: *1-6*.

Claim(s) withdrawn from consideration: _____.

8.☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☒ Other: *Notice of References Cited, PTO-892*

ADVISORY ACTION

[1] The status of the claims is as follows:

[a] Claims 1-6 are pending.

[b] Claims 1-6 stand finally rejected.

[2] The request for reconsideration in the after final amendment of Paper No. 29, filed May 12, 2003, is acknowledged and the amendment has been entered. The amendment does not place the claims in condition for allowance for the reasons stated below.

[3] The written description rejection of claims 1-6 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in previous Office actions (see item 2 of Paper No. 24 and item 1 of Paper No. 26). Applicant argues (beginning at page 7 of Paper No. 29) there should be no issue as applicant is claiming a fusion of known proteins and cite case law in support of their argument. Applicant cites Example 16 (pages 59-60) of the *Synopsis of Application of Written Description Guidelines* as further support for their argument. Applicant argues that the examiner asserts that applicant has not provided an adequate description of the function to provide structural information commonly possessed by all members of the genus. Applicant argues that the examiner's assertion that there is no way to predict other structures of those enzyme-encoding nucleic acid sequences encompassed by the genus based on those species cited in the specification is incorrect. Applicant argues enzymes are defined by their function and that examples of the claimed enzymes are known, publicly available, and have been reduced to practice. Applicant argues that, for each of the recited classes of enzymes, the amino acid sequence and encoding cDNA were known from multiple sources, and the degree of homology is such that the known nucleic acids can be used to isolate additional genes from other sources. Applicant argues methods for functional expression of the encoding sequences are disclosed in the specification as evidenced by working examples. Applicant argues methods for assaying the function of the enzymes is known. Applicant's arguments are not found persuasive. Regarding Example 16 of the *Synopsis of Application of Written Description Guidelines*, it is noted that the applicant in this example is clearly in possession of antigen X and, as generating

antibodies to a known antigen are routine, applicant has adequately described the claimed invention. In contrast to Example 16, it is the examiner's position that applicant has not described the *structures* of all species within the recited genera of enzymes. Although applicant appears to argue that the examiner takes the position the *function* of the enzymes has not been adequately described, this is not the case. The examiner acknowledges that the function of each recited enzyme is described and/or is well-known in the art based on the specification and prior art. However, as stated in previous Office actions, it is the *structures* of the enzymes that have not been adequately described. The functional definition of the genus does not provide structural information commonly possessed by all members of the genus, which distinguish the enzyme-encoding nucleic acid species within the genus such that a skilled artisan can visualize or recognize the identity of all species of recited enzymes (see page 4, lines 1-3 of Paper No. 26). Applicant argues that the degree of homology is such that the known nucleic acids can be used to isolate additional genes from other sources – however, it is noted that applicant has not demonstrated such homology or provided evidence of such homology. Even if such a "degree of homology" existed, this homology would necessarily be a comparison of *known* sequences and not those sequences yet to be isolated. Thus, the examiner's statement that "one of skill in the art would recognize that based on the disclosure of these sequences there was, and still is, no way to predict or divine the enzyme-encoding sequences from sources other than those cited in the specification" is entirely relevant to the instant rejection. Predictions based on known homology are known in the art to be unpredictable – see for example Scott et al. (*Nat Genet* 21:440-443) who teach an empirically characterized chloride-iodide transporter that, based on structural homology, is predicted to be a sulfate transporter (see particularly page 441, left column, third full paragraph). For inventions characterized by factors not reasonably predictable, which are known to one of ordinary skill in the art, more evidence is required to show possession. Based on the disclosed representative species, a skilled artisan would not be able to visualize or recognize the identity of all members of the claimed genus. Thus, given this lack of description of the structures of representative species encompassed by the genus of the claim, the specification fails to

sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

[4] The scope of enablement rejection of claims 1-6 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in previous Office actions (see item 3 of Paper No. 24 and item 2 of Paper No. 26). Applicant argues (beginning at page 4 of Paper No. 29) there is no legal requirement that applicant demonstrate reduction to practice of each possible member of encompassed within the scope of the claim. Applicant argues it is only required that applicant provide enough detail to demonstrate applicant is entitled to the entire scope of the claimed invention. Applicant argues that the teachings of the specification in combination with the state of the art provides for an enabling disclosure to make the genes required to make and use the claimed composition. Beginning at the first full paragraph of page 5, applicant argues the genes encoding all of the recited proteins are known and publicly available and can be used to isolate additional homologous genes from other sources using a number of techniques. Beginning at the first full paragraph of page 6, applicant argues methods of gene isolation are all one of skill needs to isolate any gene encoding a recited enzyme. Applicant argues common methods reveal the characteristics of homology to classify a gene as encoding an enzyme and functionality to classify the enzyme activity. Applicant argues the genes encoding the recited enzymes are well known and well characterized, the level of skill in the art is high, and it would be routine experimentation to make and use the claimed fusion enzymes. Applicant's arguments are not found persuasive. The examiner maintains his position that undue experimentation would be required for a skilled artisan to make the entire scope of claimed fusion enzymes. It is noted that the claims are not so limited to those enzymes disclosed in the specification, which are asserted to be known in the art. Instead, the claims are so broad in scope as to encompass *any* of the recited enzymes from *any* source – including those yet to be isolated. The examiner disagrees with applicant's assertion that the genes encoding all of the recited proteins are known and publicly available (see page 5, line 3 of Paper No. 29). It is noted that if the genes encoding *all* of the recited proteins, i.e., the entire scope of recited proteins, are known and publicly available, why would one need guidance for isolating

additional genes? A skilled artisan would recognize that it is highly unlikely that all of the potential genes from all sources encoding the recited enzymes have been isolated. Addressing the Factors summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)), the specification fails to provide the guidance necessary for isolating the entire scope of enzymes. For example, while applicant argues the "degree of homology is such that the known and available genes can be used to isolate additional genes from other sources encoding the enzymes" (page 4, lines 12-14 of Paper No. 29), it is noted that the specification fails to disclose those regions that are conserved throughout all of the recited enzymes that would enable a skilled artisan to generate primers or probes in order to use methods such as PCR or hybridization to isolate additional encoding sequences. In view of the lack of such guidance, there remains a high degree of unpredictability for isolating additional encoding sequences of enzymes encompassed by the scope of the claims. Furthermore, even if such guidance were provided, a skilled artisan would recognize that even though a sequence identified by PCR or hybridization due to the sequences being homologous, this is no indication that the sequences will share similar function. For example, Seffernick et al. (*J Bacteriol* 183:2405-2410) teach a first nucleic acid isolated by hybridization and PCR techniques (page 2407) that is 99% identical to a second nucleic (page 2407, right column, second full paragraph) – however, the two nucleic acids encode polypeptides having distinct functions (see title and abstract). Therefore, even though two sequences are highly homologous, it is unpredictable as to whether the sequences will encode polypeptides having similar function. Also, as stated in a previous Office action, the peptide linker of claim 1 has any number of amino acids and the peptide linker of claim 3 has from zero to fifty amino acids. Applicant has provided guidance and working examples of fusion proteins having only two amino acids linking the individual enzyme sequences. The prior art teaches that linkers from two to ten amino acids are optimal and that longer linkers are often prone to proteolytic degradation (page 230 of Bulow et al. *Trends Biotechnol* 9:226-231). Therefore, there is a high degree of unpredictability in making the claimed fusion proteins with a linker of any number of amino acids or greater than 10 amino acids in length. Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the unpredictability

in the art as evidenced by Seffernick et al. and Bulow et al., undue experimentation would be required for a skilled artisan to make the entire scope of claimed fusion enzymes.

[5] The rejection of claims 1-3, 5, and 6 under 35 U.S.C. 103(a) as being unpatentable over Peoples et al. (US Patent 5,245,023) in view of Bulow et al. (*Trends Biotechnol* 9:226-231) is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 3 of Paper No. 26). Addressing the reference of Peoples et al., applicant argues (beginning at page 10 of Paper No. 29) the fusion enzyme of Peoples et al. would not catalyze successive reactions in a PHA pathway, but alternative reactions, while the claimed fusion enzyme is a fusion of two enzymes that catalyze successive enzymatic reactions in a PHA biosynthetic pathway. Applicant argues that the enzyme of Peoples et al. does not provide an indication of the success of a fusion enzyme that catalyzes successive PHA biosynthetic pathway reactions. Addressing the reference of Bulow et al., applicant argues (beginning at the first full paragraph of page 11 of Paper No. 29) the statements of Bulow et al. are prophetic and provide no evidence to suggest a reasonable expectation of success for a fusion enzyme catalyzing successive reactions. Addressing both of the cited references, applicant argues the examiner has failed to provide evidence that one skilled in the art would have an expectation of success in fusing two catalytically active enzymes using different substrates – one of which produces the substrate for the second enzyme – in a single fusion enzyme. Applicant's arguments are not found persuasive. It is undisputed that the references of Peoples et al. and Bulow et al. teach all limitations of the claims and provide a motivation for making the claimed invention. Also, contrary to applicant's argument, the cited references provide a reasonable expectation of success for making the claimed invention. Peoples et al. teach that the product of the beta-ketothiolase (phbA) reaction, acetoacetyl-CoA, is used as a substrate for acyl-CoA reductase (phbB) to generate beta-hydroxybutyryl-CoA, which is the substrate for PHB synthase (phbC; column 1, bottom). Peoples et al. teach that co-expression of phbA, phbB, and phbC, encoding beta-ketothiolase, acyl-CoA reductase, and PHB synthase, respectively, results in the production of PHB (column 19, top). Beta-ketothiolase, acyl-CoA reductase, and PHB synthase co-expressed individually in the same host cell results in the formation of PHB, indicating that the product of

the beta-ketothiolase reaction is used as a substrate for the acyl-CoA reductase reaction and the product of acyl-CoA reductase reaction is used as a substrate for the PHB synthase reaction, i.e., the enzymes are able to catalyze successive reactions in the formation of PHB. Peoples further teaches the entire primary sequences of native beta-ketothiolase and acyl-CoA reductase from *Zoogloea ramigera* and the entire primary sequences of native beta-ketothiolase, acyl-CoA reductase, and PHB synthase from *Alcaligenes eutrophus* (see Figures 1-4). Bulow teaches that "If the entire primary sequences of the native enzymes are maintained in the fusion enzymes, the enzymes *usually* retain most of their native specific activities despite being fused together" (italics added for emphasis; page 230, left column, top). Thus, based on the teachings of Bulow et al., an ordinarily skilled artisan would recognize there is a reasonable expectation of success that two enzymes of Peoples et al. joined in a fusion would retain their respective catalytic activities and catalyze successive reactions. Furthermore, neither of the cited references presents any evidence to the contrary. Therefore, the cited references teach all claim limitations and a motivation and reasonable expectation of success for making the claimed fusion and thus the cited references render the claimed invention obvious to one of ordinary skill in the art.

[6] The rejection of claim 4 under 35 U.S.C. 103(a) as being unpatentable over Peoples et al. in view of Bulow et al. as applied to claims 1-3, 5, and 6 above, and further in view of Argos (*J Mol Biol* 211:943-958) is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a previous Office action (see item 4 of Paper No. 26). Applicant argues (pages 11-12 of Paper No. 29) the rejection is moot in view of applicant's argument addressing the rejection of claims 1-3, 5, and 6 (see item 5 above). Applicant's argument is not found persuasive. It is undisputed that the references of Peoples et al., Bulow et al., and Argos teach all limitations of the claims and provide a motivation for making the claimed invention. Furthermore, as stated above, the cited references provide a reasonable expectation of success for making the claimed fusion enzyme. Thus, the cited references teach all claim limitations and a motivation and reasonable expectation of success for making the claimed fusion and thus the cited references render the claimed invention obvious to one of ordinary skill in the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

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Art Unit 1652

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